DAYTON CHILDREN'S HOSPITAL

CLINICAL PRACTICE GUIDELINES

DISCLAIMER: This Clinical Practice Guideline (CPG) generally describes a recommended course of treatment for patients with the identified health needs. This CPG is not presented and should not be used as a substitute for the advice of a licensed independent practitioner, as individual patients may require different treatments from those specified, and guidelines cannot address the unique needs of each patient. Dayton Children’s shall not be liable for direct, indirect, special, incidental or consequential damages related to the use of this CPG.
Contact the on-call Hematologist to be consulted

Is cardiology managing the anti-coagulation for cardiac condition?

Yes → Contact the cardiology attending to be consulted

No → Discussion during consultation with hematologist and treating attending to include:
- type of anticoagulation
- time of last dose of anticoagulant
- location of bleeding
- severity of bleeding
- need for emergent invasive procedures, etc.

The agent used for reversal is based on the anti-coagulant in use and urgency of need for anticoagulation reversal

Unfractionated Heparin Infusions
- In most instances stopping the heparin infusion is sufficient for reversal as the half-life of IV heparin is 1.5 hours
- If rapid reversal of heparin is needed, then protamine sulfate can be used

Formulated: 7/2017
Reviewed: 1/2019
- Protamine Sulfate can be administered at a concentration of 10mg/mL at a rate of no more than 5 mg/min
- Patients with known allergies to fish, previous exposure to protamine sulfate, and previous exposure to protamine containing insulins are at an increased risk of hypersensitivity reactions
- PT/PTT should be obtained 15 minutes after infusion to ensure that reversal is complete
- If complete reversal is not obtained after 15 minutes, then repeat dosing may be required and should be discussed with the on call hematology attending
- If subcutaneous dosing of heparin has been used, then discussion with hematologist should occur as to how to administer protamine sulfate
- Dosing as below for IV heparin reversal:

<table>
<thead>
<tr>
<th>Time since last heparin dose</th>
<th>Dose of protamine to neutralize 100 units of heparin (amount given in last 2 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 min</td>
<td>1 mg per 100 units of heparin</td>
</tr>
<tr>
<td>30-60 min</td>
<td>0.5-0.75 mg per 100 units of heparin</td>
</tr>
<tr>
<td>60-120 min</td>
<td>0.375-0.5 mg per 100 units of heparin</td>
</tr>
<tr>
<td>&gt;120 min</td>
<td>0.25-0.375 mg per 100 units of heparin</td>
</tr>
</tbody>
</table>

**Low Molecular Weight Heparins (LMWH)**

- If immediate reversal is required, then protamine sulfate can partially reverse LMWH
- If LMWH was given in the past 4 hours, then use 1 mg protamine per 1 mg of LMWH
- Recheck PT/PTT in 2-4 hours and if prolonged a second dose of protamine sulfate at 0.5 mg per 1 mg of LMWH can be given

**Warfarin and other vitamin K antagonists**

- If no bleeding is present, then stopping warfarin is often sufficient to reverse warfarin effects but can take several days.
- INR should be followed daily to determine level of anticoagulation and response to reversal
- Level of reversal needed is determined based on need for continued anti-coagulation and if bleeding is present.
- Vitamin K Dosing:
  - No bleeding, reversal needed, and the patient will remain on warfarin, then give oral/subQ/IV dose of 0.5-2.0 mg
  - No bleeding, reversal needed, and the patient will not remain on warfarin, then give oral/subQ/IV dose of 2-5 mg
  - Bleeding that is not life threatening, then give subQ/IV dose of 2 mg
  - Bleeding that is life threatening, then give dose of 5 mg IV. Also consider giving FFP.
- FFP and prothrombin complex concentrates (PCC) can also be given for rapid reversal of VKAs. PCCs are not often available at the hospital but can be obtained from the blood bank.
• Recombinant Factor VII can be used for life-threatening bleeding (see Fact VII section below for dosing)

Direct Thrombin Inhibitors

• Dabigatran can be reversed with idarucizumab but has only been approved for adults. Adult dose is 5 mg IV once for life threatening bleeding.
• No other reversal agents available although recombinant Factor VII and PCCs have been used in life threatening bleeding in some cases
• FFP does not reverse effects

Direct Xa Inhibitors

• There are no current reversal agents available.
• Recombinant Factor VII and PCCs have been used in life threatening bleeding in some cases
• FFP does not reverse effects

Anti-platelet agents

• Anti-platelet drug effects can be present for several days to a week following cessation of the drug
• Platelet transfusion after stopping medication can reverse effects immediately
• Some evidence that DDAVP can be used to improve platelet function
  o Dosage is 0.3 mcg/kg IV once

Use of Recombinant Factor VII

• Only use for life threatening situations as there is significant risk of thrombosis with recombinant factor VII
• Discussion with hematology attending should occur prior to use of recombinant factor VII
• Dose is 90 mcg/kg IV (dose for non-life threatening bleeding is 45 mcg/kg in most cases)

Drug Dosing Sources


Dayton Children’s Hospital Medication Resource Center
DIRECT ORAL ANTICOAGULANT (DOAC)
Direct Xa Inhibitor
Rivaroxaban (Xarelto), Apixaban (Eliquis)

The following are guidelines for initiation, maintenance, monitoring, perioperative management and reversal of DOAC therapy.

All guidelines for DOAC use must be individualized for the specific patient in question. Modifications to these guidelines may be required.

I. **Initiation and Maintenance of therapy**
   A. Obtain baseline CBC, aPTT, PT, serum creatinine, and liver function tests.
   B. Patients 12 years of age and older. (Hematologist/Cardiologist will be consulted)
   C. Rivaroxaban and Apixaban dosing listed below:

   ➢ **Rivaroxaban (Xarelto) for treatment of DVT/PE**
     - 15mg twice daily with food for first 21 days, then 20mg once daily with food for remainder of treatment.
     - Avoid use in patients with CrCl < 30 ml/min.
     - Avoid use in patients with moderate to severe hepatic impairment.

   ➢ **Apixaban (Eliquis) for treatment of DVT/PE**
     - 10 mg twice daily for 7 days followed by 5 mg twice daily for remainder of treatment.
     - Avoid use in patients with CrCl < 30 ml/min.
     - Avoid use in patient with severe hepatic impairment.

II. **Monitoring of therapy**
   A. Routine coagulation testing is not required or necessary for direct oral anticoagulants (DOACs). There are currently no FDA-approved assays or calibration reagents available.
   B. Monitor renal function for patients at risk for renal dysfunction
   C. Monitor liver function at least yearly for patients receiving chronic therapy

III. **Duration of enoxaparin therapy**
   A. Duration of anticoagulation therapy is based on the clinical situation and indication for therapy.
   B. Hematologist or Cardiologist will determine appropriate length of therapy and follow-up for patient.
IV. **Perioperative Management**
A. Hold DOAC doses for 2 days prior to surgery/procedure. Consult Hematologist or Cardiologist for detailed recommendations if needed.
B. Consult the Hematologist or Cardiologist for recommendations on reinstitution of therapy.

V. **Apixaban and Rivaroxaban Reversal**
A. Andexanet alfa (Andexxa) can be used for life-threatening bleeding only after other hemostatic measures (eg, antifibrinolytic therapy [eg, tranexamic acid or aminocaproic acid] and drug removal with activated charcoal have been shown to be ineffective or when patients are at imminent risk of death from bleeding or for those who are in need of emergent surgery. Consult Hematologist for recommendations.
B. Andexxa is not available at DCH but can be obtained from Miami Valley Hospital Pharmacy if needed. Please contact Inpatient Pharmacy at x3351 if needed.
C. Recombinant Factor VII and Prothrombin Complex Concentrates (PCC) have been used in life threatening bleeding in some cases.
D. FFP does not reverse effects.

<table>
<thead>
<tr>
<th>Andexanet alfa Dose Based on Apixaban or Rivaroxaban Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FXa Inhibitor</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
</tr>
<tr>
<td>Rivaroxaban</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Low dose**: 400 mg IV bolus administered at a rate of ~30 mg/minute, followed within 2 minutes by an IV infusion of 4 mg/minute for up to 120 minutes.

**High dose**: 800 mg IV bolus administered at a rate of ~30 mg/minute, followed within 2 minutes by an IV infusion of 8 mg/minute for up to 120 minutes.

VI. **References.**
Heparin Therapy Guidelines  
(Unfractionated Heparin)

The following are guidelines for initiation, maintenance, monitoring, perioperative management and reversal of Heparin.

All guidelines for Heparin therapy must be individualized for the specific patient in question. Modifications to these guidelines may be required.

I. Initiation and Maintenance of therapy
   A. Obtain baseline CBC, aPTT and PT.
   B. Any patient with a low platelet count or an abnormal aPTT or PT should be discussed with a hematologist or cardiologist prior to starting heparin.
   C. Heparin will be dispensed by pharmacy as a pre-mixed 25,000 unit in 250 ml D5W bag for a concentration of 100 units/ml.
   D. Loading dose(s) will be bolused from the infusion bag using the bolus feature on the Alaris Smart Pump.
   E. Recommended loading dose is based on age
      i. Age < 1 year 75 units/kg IV over 10 minutes
      ii. Age ≥ 1 year 75 units/kg IV over 10 minutes (max 5000 units)
   F. Recommended initial maintenance infusion is based on age
      i. Age < 1 year 28 units/kg/hr IV
      ii. Age ≥ 1 year 20 units/kg IV (max 1000 units/hr)
   G. Subsequent infusion rates should be based on aPTT values – See Table 1. If a bolus dose or change in rate is necessary, orders must be written ASAP.

   TABLE 1.

<table>
<thead>
<tr>
<th>aPTT (seconds)</th>
<th>Bolus (units/kg)</th>
<th>Hold infusion (minutes)</th>
<th>Rate Change (units/hr)</th>
<th>Time to Repeat aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>50</td>
<td>0</td>
<td>Increase 10%</td>
<td>4 hours after rate change</td>
</tr>
<tr>
<td>50-59</td>
<td>0</td>
<td>0</td>
<td>Increase 10%</td>
<td>4 hours after rate change</td>
</tr>
<tr>
<td>60-85</td>
<td>0</td>
<td>0</td>
<td>No change</td>
<td>Next day</td>
</tr>
<tr>
<td>86-95</td>
<td>0</td>
<td>0</td>
<td>Decrease 10%</td>
<td>4 hours after rate change</td>
</tr>
<tr>
<td>96-120</td>
<td>0</td>
<td>30</td>
<td>Decrease 10%</td>
<td>4 hours after rate change</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>0</td>
<td>60</td>
<td>Decrease 15%</td>
<td>4 hours after rate change</td>
</tr>
</tbody>
</table>

II. Monitoring of therapy
   A. aPTT should be drawn 4 hour after the initial loading dose and every 4 hours until values are within 60-85 seconds on 2 consecutive checks. aPTT samples should not be drawn from the line infusing heparin.
   B. Once values are therapeutic, aPTT should be checked daily.
   C. Platelet counts should be checked daily while on heparin therapy. If platelet counts decrease by 50% or more consider the diagnosis of Heparin Induced Thrombocytopenia (HIT). Consider ordering heparin-PF4 antibodies and consulting Hematologist.
D. Duration of therapy is based on clinical situation and indication for therapy.

E. Avoid anti-platelet medications during heparin therapy such as aspirin and other NSAIDs.

F. The major adverse event to monitor during heparin therapy is bleeding. If a patient develops bleeding while on heparin therapy, stop the heparin infusion and notify the patient’s physician immediately.

III. Perioperative Management

A. Hold heparin a minimum of 6 hours prior to surgery/procedure. Consult Hematologist or Cardiologist for recommendations if needed.

B. Consult the Hematologist or Cardiologist for recommendations on reinstitution of therapy.

IV. Heparin Reversal

A. In most instances stopping the heparin infusion is sufficient for reversal as the half-life of heparin is 1.5 hours.

B. If rapid reversal of heparin is needed, then protamine sulfate can be given.

C. Protamine is administered at a concentration of 10 mg/ml at a rate not to exceed 5 mg/minute. Maximum dose of protamine is 50mg.

D. Use protamine with caution in patients allergic to fish or patients receiving protamine-containing insulin.

E. PT/PTT should be obtained 15 minutes after infusion to ensure that reversal is complete.

F. If complete reversal is not obtained after 15 minutes, then repeat dosing may be required and should be discussed with the on call Hematologist.

G. If subcutaneous dosing of heparin has been used, then discussion with Hematologist should occur as to how to administer protamine sulfate.

H. Protamine dosing below in Table 2 for IV heparin reversal.

Table 2.

<table>
<thead>
<tr>
<th>Time Since Last Heparin Dose</th>
<th>Dose of Protamine to neutralize 100 units of heparin (amount given in last 2 hours)</th>
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<tr>
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<td>0.375-0.5 mg per 100 units of heparin</td>
</tr>
<tr>
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<td>0.25-0.375 mg per 100 units of heparin</td>
</tr>
</tbody>
</table>

V. References


ENOXAPARIN (LOVENOX) THERAPY
Low Molecular Weight Heparin (LMWH)

The following are guidelines for initiation, maintenance, monitoring, perioperative management and reversal of enoxaparin therapy. All guidelines for Enoxaparin use must be individualized for the specific patient in question. Modifications to these guidelines may be required.

I. Initiation of therapy
   A. Obtain baseline CBC, INR, and aPTT.
   B. Any patient with a low platelet count or an abnormal aPTT or PT should be discussed with a hematologist or cardiologist prior to starting LMWH.
   C. Enoxaparin will be dispensed by pharmacy in a syringe as a patient specific dose. Pre-filled syringes will be utilized when possible.
   D. Recommended dosing is listed in Table 1.
   E. Subsequent dosing should be based on the anti-factor Xa level as shown in Table 2.

Table 1. Initial dosing of enoxaparin

<table>
<thead>
<tr>
<th>Treatment Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants &lt; 2 months</td>
</tr>
<tr>
<td>Infants ≥ 2 months and Children ≤ 18 years</td>
</tr>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>CrCl &lt; 30 ml/min</td>
</tr>
</tbody>
</table>

Table 2. Nomogram for enoxaparin therapy

<table>
<thead>
<tr>
<th>Anti-Factor Xa Level</th>
<th>Hold Next Dose?</th>
<th>Dose Change</th>
<th>Repeat Anti-Factor Xa Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.35 units/ml</td>
<td>No</td>
<td>Increase by 25%</td>
<td>4 hours post next dose</td>
</tr>
<tr>
<td>0.35-0.49 units/ml</td>
<td>No</td>
<td>Increase by 10%</td>
<td>4 hours post next dose</td>
</tr>
<tr>
<td>0.5-1 units/ml</td>
<td>No</td>
<td>0</td>
<td>1 x per week at 4 hours post dose</td>
</tr>
<tr>
<td>1.1-1.5 units/ml</td>
<td>No</td>
<td>Decrease by 20%</td>
<td>4 hours post next dose</td>
</tr>
<tr>
<td>1.6-2 units/ml</td>
<td>No</td>
<td>Decrease by 30%</td>
<td>4 hours post next dose</td>
</tr>
<tr>
<td>&gt; 2 units/ml</td>
<td>For these patients, all further doses should be held, and the anti-factor Xa level measured q12h until the anti-factor level is &lt;0.5 units/ml. Enoxaparin can then be restarted for patients with CrCl &gt; 30 ml/min at a dose of 40% less than was originally prescribed.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

II. Maintenance/Monitoring of therapy
   A. Monitor patients receiving therapeutic doses only. No monitoring for prophylaxis.
   B. Obtain initial anti-factor Xa level 4 hours after the 3rd or 4th dose.
   C. Based on a 4 hour level adjust dose per nomogram and repeat levels per Table 2.
   D. Monitor serial blood counts with platelets. If platelet count drops below normal, reassess therapy and consider calling Hematologist or Cardiologist.
   E. If significant bleeding occurs, hold therapy and call Hematologist or Cardiologist.

Reviewed 6/21/19
III. **Duration of enoxaparin therapy**
   A. Duration of anticoagulation therapy is based on clinical situation and indication for therapy.
   B. Hematologist or Cardiologist will determine appropriate length of therapy and follow-up for patient.

IV. **Accumulation of Enoxaparin**
   A. Some evidence suggests enoxaparin may accumulate in the body over time thus changing dosing requirements. For patients on long term therapy (> 4 weeks), this possibility should be assessed by Hematologist or Cardiologist and an Anti Xa level can be obtained on this patient population and dose adjusted per Table 2.

V. **Perioperative Management**
   A. In general hold 2 doses of enoxaparin (24 hour) prior to surgery/procedure, contact Hematologist or Cardiologist for detailed recommendations if needed.
   B. Consult the Hematologist or Cardiologist for recommendations on reinstitution of therapy.

VI. **Exonaparin Reversal**
   A. If an immediate reversal is required, protamine sulfate has not been shown to completely reverse enoxaparin but can cause partial reversal (about 70%)
   B. If enoxaparin was given in the past 4 hours, then use 1 mg protamine per 1 mg of enoxaparin
   C. Recheck PT/PTT in 2-4 hours and if prolonged a second dose of protamine sulfate at 0.5 mg per 1 mg of enoxaparin can be given
   D. The maximum dose of protamine, regardless of the amount of enoxaparin received is 50 mg.
   E. Protamine is administered at a concentration of 10 mg/ml at a rate not to exceed 5 mg/minute. Rapid infusion can cause hypotension.
   F. Use protamine with caution in patients allergic to fish or patients receiving protamine-containing insulin.

VII. **References**
WARFARIN THERAPY
Vitamin K Antagonists (VKA)

The following are guidelines for initiation, maintenance, monitoring, perioperative management and reversal of warfarin therapy.

All guidelines for Warfarin use must be individualized for the specific patient in question. Modifications to these guidelines may be required.

I. **Initiation of therapy**
   A. Obtain baseline (pre-warfarin treatment) INR. Consider also obtaining liver function tests if liver dysfunction is a possibility (specifically including PTT, AST, ALT, alkaline phosphatase, and total and direct bilirubin).
   B. Most patients require 3 to 5 days of loading doses until a stable maintenance phase is achieved.
   C. Day 1 loading dose is 0.2 mg/kg orally as a single daily dose (maximum dose = 10 mg). If liver dysfunction present, baseline INR > 1.2, or patient has a Fontan-type cardiac surgery palliation, consider starting dose of 0.1 mg/kg orally as a single daily dose (maximum dose = 5mg)
   D. Subsequent doses should be based on INR response- see Table 1.
   E. At the discretion of the attending physician alternative anticoagulation therapy may be advisable prior to warfarin initiation

   **TABLE 1: DAYS 2 – 4 WARFARIN LOADING DOSES**

<table>
<thead>
<tr>
<th>INR</th>
<th>warfarin adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 - 1.3</td>
<td>repeat initial loading dose</td>
</tr>
<tr>
<td>1.4 - 1.9</td>
<td>50% of initial loading dose</td>
</tr>
<tr>
<td>2.0 - 3.0</td>
<td>50% of initial loading dose</td>
</tr>
<tr>
<td>3.1 - 3.5</td>
<td>25% of initial loading dose</td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>hold warfarin until INR &lt; 3.5 then restart at 50% less than previous dose</td>
</tr>
</tbody>
</table>

II. **Maintenance of therapy**
   A. For medically stable patients on long-term warfarin therapy, the INR should be tailored for the condition being treated. For example, many patient conditions require INR to be between 2.0 and 3.0 inclusive, but with mechanical heart valves, the INR may be allowed to be as high as 3.5.
   B. Duration of therapy is dependent on the primary problem.
   C. Hematologist or Cardiologist will determine appropriate length of therapy and follow-up for patient.
   D. Dosing – see Table 2.
TABLE 2: CHRONIC WARFARIN THERAPY

<table>
<thead>
<tr>
<th>INR</th>
<th>warfarin adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 – 1.4</td>
<td>increase dose by approximately 20%</td>
</tr>
<tr>
<td>1.5 – 1.9</td>
<td>increase dose by approximately 10%</td>
</tr>
<tr>
<td>2.0 – 3.0*</td>
<td>no change</td>
</tr>
<tr>
<td>3.1 – 3.5</td>
<td>decrease dose by approximately 10%</td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>hold warfarin until INR &lt; 3.5 then restart at 20% less than previous dose</td>
</tr>
<tr>
<td>* (or 3.5 if mechanical cardiac valve)</td>
<td></td>
</tr>
</tbody>
</table>

III. Monitoring of chronic warfarin therapy
A. Monitor INR after changing doses (typically no sooner than 2 days and within 7 days of dose change).
B. Once dosage stability is achieved with weekly INR monitoring, the INR monitoring interval can be lengthened to 2 weeks, then 3 weeks, and eventually 4 weeks. Most patients require a minimum of monthly INR evaluations.

IV. Perioperative Management
A. Hold warfarin doses 3-5 days prior to surgery/procedure for patients on chronic therapy who are at low risk. Patients at high risk may need to be bridged with heparin. Consult Hematologist or Cardiologist for detailed recommendations if needed.
B. Consult the Hematologist or Cardiologist for recommendations on reinstitution of therapy.

V. Warfarin Reversal
A. Level of reversal needed is determined based on need for continued anticoagulation and if bleeding is present.
B. Reversal products are Vitamin K, FFP, prothrombin complex concentrates (PCC) and Recombinant Factor VII. Refer to detailed instructions located in the CPG for Anticoagulation Reversal.

VI. References